An Extrapolation Approach to Aprepitant Pediatric Drug Development

Anne Chain[1]; Leila Kheibarshekan[2]; Rebecca Wrishko[3]; Nathalie H Gosselin[2]
[1]Merck Research Laboratories (Rahway, NJ), Merck & Co., Inc., Kenilworth, NJ, USA;
[2]Certara, Montreal, Canada; [3]Merck Research Laboratories (Upper Gwynedd, PA), Merck & Co., Inc., Kenilworth, NJ, USA

BACKGROUND

According to US and EU regulatory agencies, pediatric extrapolation approaches may be warranted "if course of the disease and effects of the drug are sufficiently similar in adults and pediatric patients, [it] may be concluded that pediatric effectiveness can be extrapolated **from adequate and well-controlled studies in adults**, usually supplemented with other information obtained in pediatric patients…". Also, "a study may not be needed in each pediatric subpopulation if data from one subpopulation can be extrapolated to another."

Chemotherapy-induced nausea and vomiting (CINV) continues to be one of the most undesirable side effects in patients undergoing cancer treatment. Current clinical practice guidelines for children undergoing chemotherapy recommend the use of a 5-HT3 antagonist, such as ondansetron, and a corticosteroid to alleviate nausea and vomiting associated with emetogenic chemotherapy. Despite the widespread availability of these agents, nausea and vomiting continue to occur and remain a major source of distress for pediatric oncology patients and their families. Thus, there is an ongoing need to evaluate new antiemetic agents, such as fosaprepitant, to alleviate CINV in children receiving emetogenic chemotherapy. A pediatric development program is being conducted to evaluate the use of intravenous (IV) fosaprepitant for the prevention of nausea and vomiting associated with highly and moderately emetogenic chemotherapy in pediatric patients.

OBJECTIVES

- Identify an appropriate 1-day intravenous (IV) dose of fosaprepitant in pediatric subjects that provides exposures similar to those associated with efficacy in adults
- Identify a 3-day combined IV/oral fosaprepitant and aprepitant regimen that provides exposures similar to the approved pediatric 3-day oral regimen of aprepitant

METHODS

Figure 1. Overview of Population PK Modeling and Simulations of Fosaprepitant in Pediatric Patients

Structural Population PK Model

2 compartment, linear elimination, first-order absorption rate, and lag time of absorption for aprepitant administration, with formulation effect on lag time (ie, suspension vs capsule) and WT effect PK parameters (ie, 0.75 for CL/Q and 1 for V2/V3) based on previous population PK model

↓

Covariate Analysis

Evaluation of covariate trends using scatter matrix plots for continuous variables and boxplots for categorical covariates with individual random effect of Ka, CL, V2, Q, V3

↓

Final Model With Updated Data

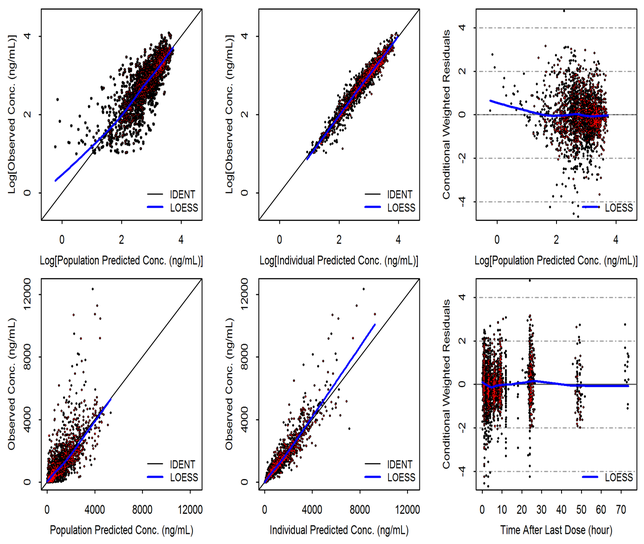
Model qualification with goodness-of-fit plots and exploratory covariate plots to detect remaining trends

↓

Monte Carlo Simulations for Aprepitant/Fosaprepitant in Pediatric Population

PK exposure levels for single 1-hr fosaprepitant infusion in pediatric population (0.5-<12 years old) and for 3 days of regimens of aprepitant/fosaprepitant in pediatric population (0.5-19 years old). Patient characteristics in the PK population and final population PK model were used to derive the simulated profiles of aprepitant

Figure 2. Goodness of Fit: Final Population PK Model of Aprepitant



Conc, concentration; IDENT, identity line; LOESS, locally weighted scatter plot smoothing; PK, pharmacokinetic

Note: Observed concentrations vs population and individual predicted concentrations are presented on log scales in the upper left and upper central plots, respectively, and in linear scales in the lower left and lower central plots, respectively.

Note 1: Red dots are for samples in Study P029.

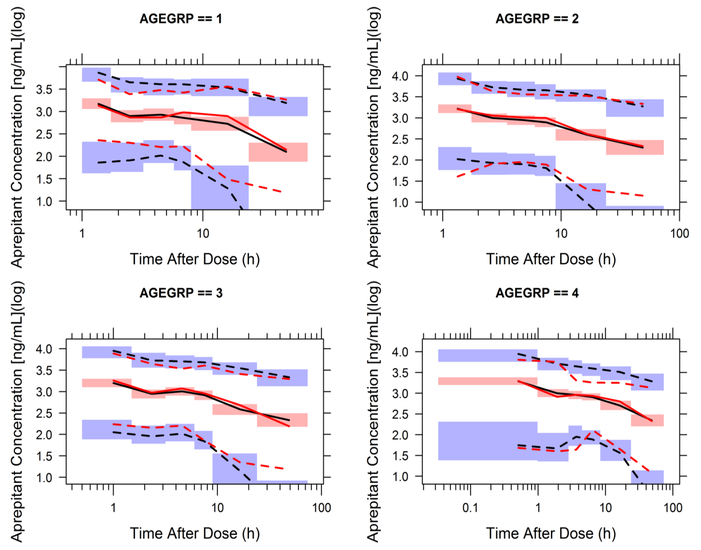
Note 2: One sample with CWRES of -7.20 (SUBJID#104923 at 0.5 hr after the dose, in Study P029).

RESULTS

Figure 3. Visual Predictive Check for Fosaprepitant Administration by Age Group of Pediatric Population – Log Scale

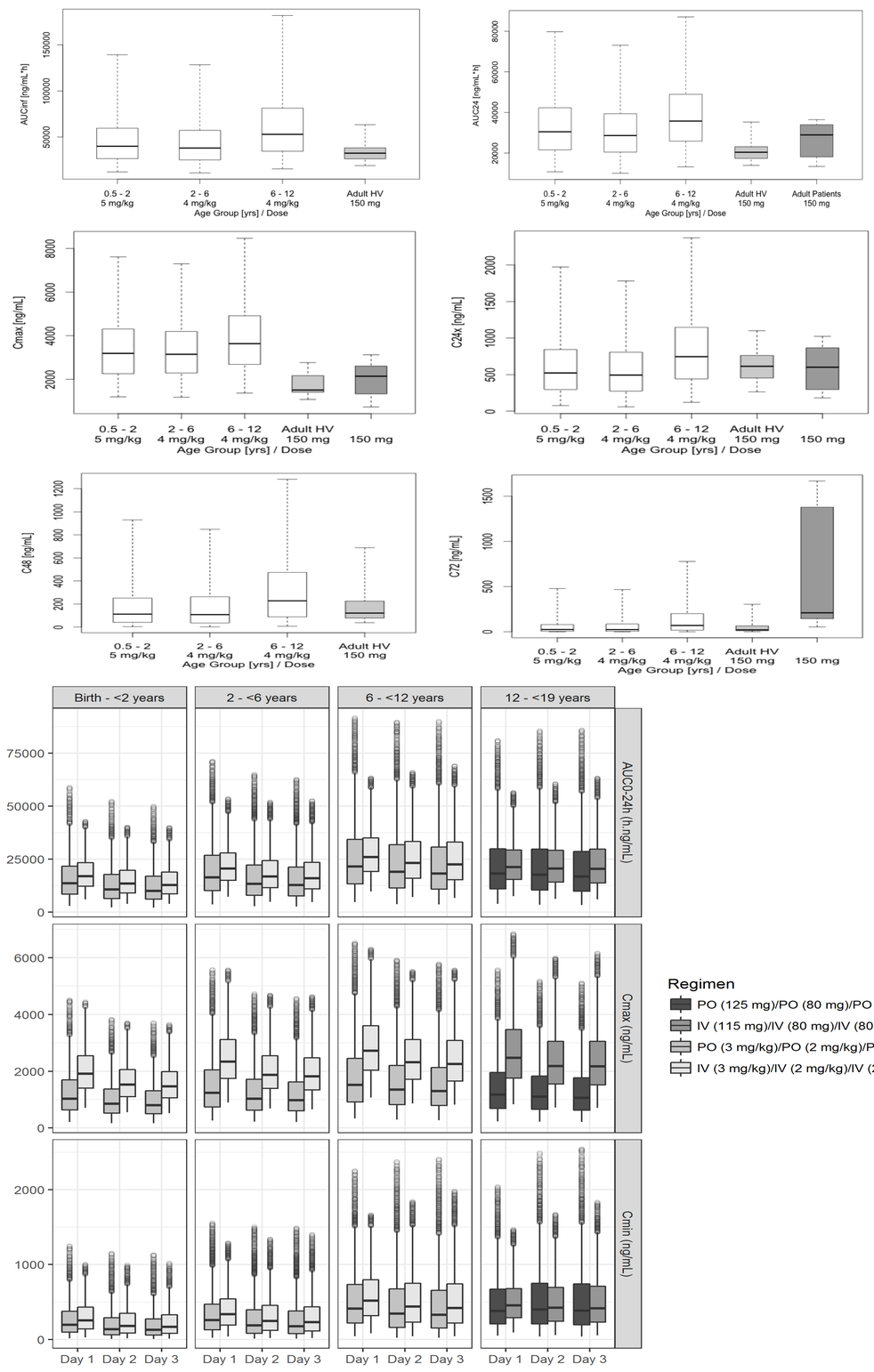
AGEGRP, age group; AGEGRP=1, subjects <2 years of age; AGEGRP=2, subjects 2 to <6 years of age; AGEGRP=3, subjects 6 to <12 years of age; AGEGRP=4, subjects 12 to ≤19 years of age.

Full and dashed red lines represent 2.5th, 50th, and 95th percentiles of observed aprepitant concentrations within each bin; shaded areas represent 95% percentile interval of percentiles of predicted concentrations (50th percentiles are in red and 2.5th and 97.5th percentiles are in blue). Note 3: 6 bins were generated, with equal counts of observation per bin.



A 2-compartment model was found to be appropriate to describe the modeling data. Based on exposure levels observed in adults after a single IV dose of fosaprepitant, Figure 4 (top) shows that regimens of 5 mg/kg and 4 mg/kg were appropriate for subjects 6 months to <2 years old and 2 to <12 years old, respectively. Bottom panel shows that regimens of 115 mg on Day 1 and 80 mg on Days 2 and 3 in adolescents, as well as 3 mg/kg on Day 1 and 2 mg/kg on Days 2 and 3 in subjects <12 years old, were adequate for a 3-day IV /oral regimen.

Figure 4. Distribution of PK Parameters for Optimal 1-Day (top) and 3-Day (bottom) Fosaprepitant Regimens in Patients Aged 0.5-<12 Years Old



CONCLUSIONS

Appropriate 1-day IV doses of fosaprepitant were identified for pediatric subjects. These results supported an extrapolation approach in the 1-day IV setting using model-based evaluations to ascertain a dosing recommendation, which facilitated the early termination of a Phase 3 trial. In addition, a successful bridging strategy was also used to find a 3-day IV/oral regimen for use in children.